

Claims:

1. A method for synthesis of 4',4-bis-{4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino}-biphenyl-2,2'-disulfonic acid, the
5 process comprising the steps of:

a) reacting 2-(3-Nitro-benzenesulfonylamino)-acetamide with N,N-Dimethyl-formamide in the presence of $\text{ClCH}_2\text{CONH}_2$ and a base to provide 2-[Carbamoylmethyl-(3-nitro-benzenesulfonyl)-amino]acetamide;

10 b) treating the 2-[Carbamoylmethyl-(3-nitro-benzenesulfonyl)-amino]-acetamide product of step a) with a reducing agent to provide 2-[(3-Amino-benzene-sulfonyl)-carbamoylmethyl-amino]acetamide;

15 c) treating the 2-[(3-Amino-benzene-sulfonyl)-carbamoylmethyl-amino]-acetamide product of step b) with cyanuric chloride to give 2-[(4-{4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide; and

20 d) reacting the 2-[(4-{4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide product of step c) with the disodium salt of 4,4'-diamino-2,2'-biphenyldisulfonic acid.

2. The method of Claim 1 wherein the treatment of 2-[(3-Amino-benzene-sulfonyl)-carbamoylmethyl-amino]acetamide with cyanuric chloride to give 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzene-sulfonyl)-carbamoylmethyl-amino]acetamide is conducted at a temperature of from about 20°C to about 25°C.

3. The method of Claim 1 wherein the treatment of 2-[(3-Amino-benzene-sulfonyl)-carbamoylmethyl-amino]acetamide with cyanuric chloride to give 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzene-sulfonyl)-carbamoylmethyl-amino]acetamide is conducted in a reaction medium containing 1-methyl-2-pyrrolidinone and sodium carbonate or sodium bicarbonate.

4. The method of Claim 1 further comprising the step of recrystallizing the 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide product of step c) from a mixture of
5 1-methyl-2-pyrrolidinone and water prior to completing the reaction of step d).

5. The method of Claim 1 wherein step d) is conducted at a temperature of from about 15°C to about 90°C.

10 6. The method of Claim 5 wherein step d) is conducted at a temperature of from about 60°C to about 75°C.

15 7. The method of Claim 1 wherein step d) is conducted in a medium comprising dimethyl sulfoxide.

15 8. A method for preparation of 2-[Carbamoylmethyl-(3-nitro-benzenesulfonyl)-amino]acetamide, the method comprising reacting 2-(3-Nitro-benzenesulfonylamino)-acetamide with N,N-Dimethylformamide in the presence of CICH₂CONH₂ and a base.

20 9. The method of Claim 8 wherein the base is sodium carbonate, potassium carbonate or sodium bicarbonate.

25 10. The method of Claim 8 further comprising an initial step of preparing 2-(3-Nitro-benzenesulfonylamino)-acetamide by reacting 3-Nitro-benzenesulfonyl chloride with aminoglycine hydrochloride or its free base in a basic reaction medium.

11. The compound 2-(3-Nitro-benzenesulfonylamino)-acetamide.

30 12. A process for purifying 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide obtained by treating 2-[(3-amino-benzenesulfonyl)-carbamoylmethyl-amino]acetamide with cyanuric chloride, which comprises dissolving 2-[(4-{4-[4-(bis-

carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide in a volume of water and 1-methyl-2-pyrrolidinone, followed by addition of excess water to precipitate a more purified amount of 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-

5 benzenesulfonyl)-carbamoylmethyl-amino]acetamide.

13. A process according to claim 12 wherein the ratio of water:1-methyl-2-pyrrolidinone into which the amount of 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]-

10 acetamide is dissolved is from about 1:1 by weight.

14. A process according to claim 12 wherein precipitation of the desired 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide product is carried out by adding 15 additional water to create a water:1-methyl-2-pyrrolidinone ratio of up to about 6:1 (wt:wt),

15. A process according to claim 13 wherein precipitation of the desired 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide product is carried out by adding 20 additional water to create a water:1-methyl-2-pyrrolidinone ratio of up to about 6:1 (wt:wt),

16. A process according to claim 14 wherein precipitation of the desired 2-[(4-{4-[4-(Bis-carbamoylmethyl-sulfamoyl)-benzyl]-6-chloro-[1,3,5]triazin-2-ylmethyl}-benzenesulfonyl)-carbamoylmethyl-amino]acetamide product is carried out by adding 25 additional water to create a water:1-methyl-2-pyrrolidinone ratio from about 3:1 to about 5:1 (wt:wt).

30 17. A process for the increasing the purity of 4',4-bis-{4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino}-biphenyl-2,2'-disulfonic acid, disodium salt which comprises dissolving impure 4',4-bis-{4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino}-biphenyl-2,2'-

disulfonic acid, disodium salt in volume of acetonitrile-water having a mixture ratio of from about 0.75:2 to about 1.5:2 by volume at an elevated temperature, such as from about 30°C to about 70°C, followed by addition of additional acetonitrile until crystallization of the desired compound is achieved.

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18. A process according to Claim 17 wherein the elevated temperature is from about 65°C - about 70°C and after the addition of additional acetonitrile the mixture is cooled to about 49°C - about 51°C.

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19. A process according to claim 1 in which the 4',4-bis-[4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino]-biphenyl-2,2'-disulfonic acid, disodium salt prepared is purified by dissolving impure 4',4-bis-[4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino]-biphenyl-2,2'-disulfonic acid, disodium salt in volume of acetonitrile-water having a mixture ratio of from about 0.75:2 to about 1.5:2 by volume at an elevated temperature, such as from about 30°C to about 70°C, followed by addition of additional acetonitrile until crystallization of the desired compound is achieved.

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20. A process according to claim 19 in which the 4',4-bis-[4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino]-biphenyl-2,2'-disulfonic acid, disodium salt prepared is purified by dissolving impure 4',4-bis-[4,6-bis-[3-(bis-carbamoyl-methyl-1-sulfamoyl)-phenylamino]-[1,3,5]triazin-2-ylamino]-biphenyl-2,2'-disulfonic acid, disodium salt in volume of acetonitrile-water having a mixture ratio of from about 0.75:2 to about 1.5:2 by volume at an elevated temperature of from about 65°C to about 70°C, followed by addition of additional acetonitrile and cooling of the mixture to a temperature of from about 49°C to about 51°C until crystallization of the desired compound is achieved.

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